Microreviews in Cell and Molecular Biology 2012

Protein Synthesis Inhibitors Effects on Long-Term Memory

Author: Kyle Michelsen
Major:
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words: Protein synthesis, memory, inhibitors, long-term

The model for the molecular basis of memory is that memory formation occurs in two stages. There is an early temporary stage independent of protein synthesis and a long-term memory phase dependent on training-initiated de novo protein synthesis. The stage pertaining to the formation of long-term memory has been thoroughly researched in numerous studies through the injection of drugs, which inhibit protein synthesis in the brain. The inhibition of protein synthesis has shown little effect on short-term memory but greatly impairs the formation of long-lasting memories. However, some recent studies have attempted to nullify the effects of protein synthesis inhibitors. These studies have demonstrated a weakening in amnesia generated by protein synthesis inhibitors through the use of stimulant drugs, local anesthetics, and inhibitory avoidance training to counteract the effects of the inhibitor. Consequently, the resulting attenuation observed in these instances is not consistent with the contemporary view that protein synthesis initiated by training is necessary for memory formation.

Introduction

The modern theories for memory formation depicts protein synthesis being initiated by a form of training as a required mechanism for neural plasticity, the changing of the structure, function, and organization of neurons in response to new experiences. These theories are supported by research studies that impaired the formation of long lasting memories through interrupting protein synthesis with protein synthesis inhibitors like anisomycin. However, findings in recent studies have brought about an alternative interpretation for the cause of the resulting amnesia. This alternative interpretation states the release of an abnormally large amount of neurotransmitters at the injection site of the protein synthesis inhibitor, is responsible for the resulting amnesia. Furthermore, this suggests that protein synthesis inhibitors act on memory by altering modulators of memory formation as a secondary consequence of the inhibition of protein synthesis rather than the requirement of training-initiated synthesis of proteins required for memory formation [1]. Since, modulators of memory formation emphasize the roles of hormones and neurotransmitters in regulating memory function.

Recent Progress

In the brain, the amygdala is the location of memory formation and is also believed to modulate memories formed elsewhere in the brain. Due to the amygdala being the location of memory formation, research studies generally use this location as the insertion site for protein synthesis inhibitors. For instance, in a recent study the intra-amygdala was injected with a B-andrenergic receptor antagonist propranolol before the treatment was administered and was found to significantly attenuate anisomycin-induced amnesia. In this experiment, a vivo microdyalysis was used to measure the release of the different neurotransmitters before and after the injections. When the intra-amygdala was injected with the protein synthesis inhibitor anisomycin, it resulted in amnesia and an abnormal increase in the release of norepinephrine, dopamine, and serotonin in the amygdala [2]. These results suggest that the abnormally large increases in neurotransmitter released after injection of a protein synthesis inhibitor may be the actual cause of the drug-induced amnesia.

The alternative interpretation supported by the results of the experiment previously mentioned has promoted further research studies in furthering our

knowledge of the cause of amnesia. In a recent study, the local anesthetic lidocaine and the protein synthesis inhibitor anisomycin were administered prior to inhibitory avoidance training, in an attempt to attenuate the resulting amnesia by lessoning the effect of the neurotransmitter norepinephrine. As shown in previous studies, the injection of the anisomycin produces abnormally large amounts of the neurotransmitter norepinephrine in the amygdala. Also, norepinephrines effects on memory are found to follow an inverted U relationship with memory formation. However, in this study the treatment of the anesthetic lidocaine was found to effectively block the increase in release of norepinephrine at the amygdala site of anisomycin injection [3]. Thus, the pretreatment of lidocaine can effectively attenuated the anisomycin-produced amnesia of memory by inhibiting the release of neurotransmitters.

As previously mentioned, the inhibitory avoidance training, a shock given to the specimen's foot, was administered during the experiments to investigate the protein synthesis inhibitors effect on memory. Inhibitory avoidance training is used because increased foot shock levels have been found to protect against amnesia in both mice and rats. Nevertheless, until a recent experiment, the effects on memory at different dosages of protein synthesis inhibitor and inhibitory avoidance training at various shock intensities had not been examined. In this study, two experiments were carried out. In the first experiment, mice were injected with either the protein synthesis inhibitor cycloheximide or a saline solution and then proceded with inhibitory avoidance training at various shock intensities to examine its affects on memory. In the second experiment, the mice were trained with one shock intensity but were given injections of saline and cycloheximide at various dosages. The saline injection was used to act as a control in testing if the inhibitory avoidance training increased memory latency. The first experiment resulted in increased memory latencies as a function of shock intensity. It also demonstrated that cycloheximide's ability to impair memory increases as training shock intensity is increased. The second experiment resulted in cycloheximide enhancing memory in an Inverted-U-dose response manner that was consistent with previous findings. The results obtained suggest that protein synthesis inhibitors act on memory by altering modulators of memory formation as a secondary consequence of the inhibition of protein synthesis rather than by with training-initiated synthesis of proteins required for memory formation [1].

Discussion

Prior studies have shown that when protein synthesis inhibitors are injected into the brain it impairs the formation of long-lasting memories. This finding has led us to our current molecular model for memory formation that depicts the formation of long-term memory being dependent on training-initiated de novo protein synthesis. However, results obtained from the studies previously mentioned contradict our current model and have led to an alternative interpretation.

The alternative interpretation suggests that the impairments of memory with protein synthesis inhibitors is not a function of impairment of training-related proteins needed for memory formation but instead a by-product of actions of protein synthesis inhibitors and perhaps interference with the functions of neuromodulators [1]. The finding that an injection of a protein synthesis inhibitor results in a large increase in the release of several neurotransmitters at the injection site supports this interpretation. Norepinephrine, one of the several neurotransmitters released, was found to be an important element in the modulation of memory formation. Suggesting that the abnormal release of norepinephrine in response to the protein synthesis injection plays a major contributor to the resulting amnesia. This interpretation is further supported by the finding that lidocaine attenuates anisomycin-induced amnesia by preventing the release of norepinephrine in response to being injected with a protein synthesis inhibitor. In addition, the evidence of high shock intensities being able to counteract the effects of protein synthesis inhibitors on memory supports the alternative interpretation.

The findings found in the studies mentioned have led to answers that have been left unanswered for decades. However, with each new finding presents multiple new questions that are left unanswered. For instance, why do protein synthesis inhibitors not influence short-term memory? Does protein synthesis occur in certain kinds of cells found in the brain? What is the mechanism for forgetting? In other words, after more than fifty years of research little is still known about the molecular level of how memories persist.

References

[1] Gold, Paul E., and Sean M. Wrenn. "Cycloheximide Impairs and Enhances Memory Depending on Dose and Footshock Intensity." Behavioral Brain Research 233.2 (2012): 293-97. Print.

[2] Qi, Z., and P. E. Gold. "Intrahippocampal Infusions of Anisomycin Produce Amnesia: Contribution of Increased Release of Norepinephrine, Dopamine, and Acetylcholine." Learning & Memory 16.5 (2009): 308-14. Print.

[3] Sadowski, Renee N., Clint E. Canal, and Paul E. Gold. "Lidocaine Attenuates Anisomycin-induced Amnesia and Release of Norepinephrine in the Amygdala." Neurobiology of Learning and Memory 96.2 (2011): 136-42. Print.

